

Criteria for early congenital syphilis— a perspective from Africa

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Introduction

Despite recent advances in serology, the diagnosis of congenital syphilis still presents difficulties.¹ *Treponema pallidum* cannot be grown in vitro and in the majority of cases the organism is not readily identifiable. Clinical findings may be absent; approximately two-thirds of the cases are asymptomatic at birth.^{2,3} Serology also has limitations in that it may not distinguish between antibodies from the mother and those from the infant. Tests relying on the presence of IgM immunoglobulins allow detection of antibodies derived exclusively from the infant but the sensitivity of such tests has not been definitely established. Follow-up to monitor clinical and serological features is more definitive but outpatient attendance may be difficult to ensure. These problems mean that no "gold standard" test can be applied and this in turn leads to uncertainties regarding case definition and reporting.

In order to overcome these problems a combination of clinical, epidemiological and serological features is used to categorise infants with syphilis. Apart from assisting with diagnosis, the classification of congenital syphilis is important for surveillance purposes, to facilitate comparison, to determine treatment guidelines and to enable prognostication. The most recent proposals are from the Centers for Disease Control (CDC) and are expressly designed for case reporting and surveillance.⁴ In practice, however, the same guidelines are used to determine which cases need treatment.⁵

The purpose of this review is to discuss the various criteria and their applicability in third world situations. It is proposed that in these circumstances, the classification of Kaufman *et al*⁶ which was in use by the CDC prior to 1988, is the most suitable from a diagnostic and therapeutic point of view.

Syphilis in pregnancy in Africa

Most of the classification systems have been designed in countries where the health care system is relatively well established. However, underdeveloped countries—including many parts of Africa—have particular problems of their own. The prevalence of seropositive pregnant women is high—at least 10% if one considers nontreponemal tests.⁷ One study reported that up to 44% of antenatal cases had positive treponemal tests and may have had active syphilis.⁸ As many as 25% of pregnant women deliver before receiving antenatal care so that their serology for syphilis is unknown.⁹

Attendance at antenatal clinics late in pregnancy is common; for example 85% of mothers had their first visit after 20 weeks in Zambia.¹⁰ This allows insufficient opportunity for the evaluation of the effectiveness of therapy in pregnancy. Furthermore, compliance with treatment is poor; only 10% of women completed their prescribed treatment at a teaching hospital.¹¹

Early congenital syphilis

The problems of inadequate diagnosis and treatment of syphilis in pregnancy outlined above have resulted in a failure to prevent transmission to the fetus. A third of infected infants will have clinical signs at birth, the remainder being asymptomatic initially. In the light of these facts, how useful are the different criteria?

Symptomatic infants

CDC Criteria Infants with clinical signs would be placed in the "presumptive" category, along with asymptomatic cases (see *Appendix*). The prognosis in these two groups is vastly different¹² and the clinical comparison between cases and different studies is therefore difficult. This problem has arisen because the groups defined by the CDC were not designed primarily for diagnosis or treatment but for case reporting and this limits the clinical usefulness of the divisions.

An additional drawback is that some of the diagnostic features are nonspecific. Positive treponemal tests are frequent in Africa and periosteal reactions have been reported in 35% of normal term infants.¹³ Likewise, clinical features such as hepatosplenomegaly may occur in conditions apart from congenital syphilis.¹⁴

Assuming that a stillbirth is due to congenital syphilis because of positive STS alone (see *Appendix*) is also likely to be nonspecific as over 40% of mothers have positive treponemal tests in some localities.⁸ In all probability a significant number of these mothers have late syphilis and stillbirths could theoretically be expected in 10% of such pregnancies.¹⁵

The case definitions of Kaufman *et al* (1977) Kaufman and colleagues developed a classification in which infants were designated as definite, probable, possible or unlikely cases. Unlike the CDC guidelines, a distinction can be made between asymptomatic (possible) and clinically apparent (probable) cases in the first months of life (table). In common with the CDC criteria, the features could be non-specific where positive treponemal tests are

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frequent. Additional drawbacks are: (1) no provision is made for the 10% or so of cases of congenital syphilis that are symptomatic but have negative nontreponemal tests at birth,¹⁶ (2) stillbirths are not included.

Other classification systems Mascola and co-workers spelt out that cases with one of the minor clinical signs of Kaufman *et al* should be placed in the “possible” group.¹⁶ The reason for this modification is not clear as such a classification was implicit in the original paper of Kaufman *et al*.

Rathbun's diagnostic criteria for congenital syphilis include clinical, serologic and epidemiologic features which in turn are subdivided into major and minor categories.¹⁷ There are a number of nonspecific minor clinical features such as growth retardation. Small for gestational age babies are common in underdeveloped localities and accounted for 6% of otherwise normal newborns in one study.¹⁸ Furthermore, congenital syphilis does not appear to influence fetal growth.¹⁹ The only major epidemiological criterion is untreated early syphilis in the mother. Unfortunately the stage of the disease in pregnancy is often unknown so that identifying these mothers could be difficult.²⁰

Hira *et al* have published guidelines for the diagnosis of congenital syphilis in developing countries.²¹ Essentially the proposals are similar to those of Kaufman *et al* except that the minor clinical manifestations (hepatosplenomegaly, jaundice, anaemia, radiologic abnormalities, cerebrospinal fluid changes) are given an equal weighting to the major. The rationale for this is that in Zambia (where a variety of congenitally acquired infections are common), the minor signs were more frequent in infants with positive serological tests for syphilis (STS) than those without. For this observation to be valid, however, it is necessary that the prevalence of the different congenital infections is the same as that of syphilis and that

infected infants develop symptoms at a similar age. Such conditions have not been shown to exist. A useful feature of the classification is that it is one of the few to take into account the possibility of infection in an infant with negative serology at birth.¹⁶

Asymptomatic infants

In underdeveloped countries a common and difficult management problem is posed by infants who appear healthy at birth but whose mothers had reactive STS and were not adequately treated in pregnancy.

Applying the CDC criteria Such cases fall into the category designated “presumptive case” by the CDC (*Appendix*). It is unlikely that all these infants do, in fact, have congenital syphilis. In a recent study 66 neonates born to mothers who were untreated or inadequately treated in pregnancy were followed-up.²² Infants were regarded as uninfected if there were no clinical signs and Venereal Disease Research Laboratory (VDRL) titres had declined to zero over a 3–4 month period. There was one case of congenital syphilis amongst 18 whose mothers either received benzathine penicillin in the last month of pregnancy or were treated with erythromycin. Amongst the infants of the 48 untreated mothers 14 infants developed congenital syphilis. According to CDC criteria all 66 infants would have been regarded as compatible cases (an 18-fold increase in the treated group and a 3·5-fold increase in the untreated group). This indicates that using these CDC criteria will result in overdiagnosis. It may be that the guidelines provide too sensitive an index where incomplete or unknown treatment status of the mother is common.

Case definitions of Kaufman *et al* In this system provision is made for asymptomatic cases—the majority of well infants born to mothers with inadequately treated syphilis would be classi-

Table *Criteria for the diagnosis of neonatal and early congenital syphilis (Kaufman *et al* 1977)

Diagnostic criteria	
Clinical	
Absolute	
(1) Specimen from lesions showing presence of <i>T. pallidum</i> by dark-field examination, or by histologic examination	Serologic
Major	
(2) Condyloma lata	A. Reactive STS (VDRL or FTA-ABS)
(3) Osteochondritis, periostitis	B. Reactive FTA-ABS (IgM) Test
(4) Snuffles or hemorrhagic rhinitis	C. Nonreactive STS (VDRL and FTA-ABS)
Minor	
(5) Fissures of lips	D. Reactive STS (VDRL or FTA-ABS) that does not revert to nonreactive within 4 months
(6) Cutaneous lesions	E. Rising VDRL titer over 3 months
(7) Mucous patches	Maternal History
(8) Hepatomegaly, splenomegaly	AA. Documented history of adequately treated syphilis during pregnancy
(9) Generalized lymphadenopathy	
(10) Central nervous system signs	
(11) Hemolytic anemia	
(12) Elevated cells or protein in cerebrospinal fluid	
Certainty of Diagnosis	
Definite—Absolute clinical criterion	
Probable—Any of the following: (1) Serologic criterion E; (2) Serologic criterion D; (3) One major clinical criterion and serologic criterion A or B; (4) Two or more minor clinical criteria and serologic criterion A or B; (5) One major and one minor clinical criterion.	
Possible—Serologic criterion A or B without clinical criterion	
Unlikely—(1) Serologic criterion C with any other criterion; (2) Serologic criterion A or B with maternal history AA.	
STS—Serologic Test for Syphilis	
VDRL—Venereal Disease Research Laboratory Test	
FTA-ABS—Fluorescent Treponemal Antibody-Absorption Test	
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fied as "possible" cases.

A potential problem is the statement that the STS should revert to nonreactive by 4 months in uninfected cases (table). Several authorities, including the CDC, regard 6 months as the outside limit for cardiolipin tests to become negative.^{4,12}

Other classification systems The proposals of Rathbun and Hira *et al* do not make provision for asymptomatic, at risk infants.

Conclusions

Unfortunately none of the proposed systems are perfect and changes are likely as new tests become available. In choosing the most appropriate case definitions it is necessary to decide if the primary need is for diagnosis or surveillance. The CDC recommendations high-light a public health problem and target a high risk population; in fact treatment is being suggested for these patients. This may be safer, but overtreatment is likely with unnecessary use of resources.

From a diagnostic and therapeutic point of view the proposals of Kaufman *et al* seem to have advantages for underdeveloped countries. These workers have defined the "probable" cases more strictly and thus infants who definitely require therapy are identified.

The "possible" cases (that is, apparently healthy infants with positive STS) whose mothers had inadequate treatment remain a difficult management problem. Infants at greatest risk appear to be those whose mothers have high titres of nontreponemal tests and where no treatment was received in pregnancy.²² Ten to 14 days of penicillin therapy (either crystalline penicillin 100,000-150,000 units/kg/day or intramuscular procaine penicillin 50,000 units/kg/day) should be given to these infants. In the follow-up study cited above this approach would have effectively treated all infected cases. Simple investigations such as testing for rheumatoid factor and measuring total IgM levels may also be helpful in making decisions at birth.³

Local resources and the prevalence of HIV infection influence the management of the remaining lower risk group. It has been our practice to recommend one injection of benzathine penicillin (50,000 units/kg intramuscularly) in these cases.

In summary, the CDC guidelines simplify surveillance but the classification of Kaufman *et al* is more helpful in a clinical setting where large numbers of patients fulfil the criteria for case reporting.

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Appendix

Congenital Syphilis Surveillance Case Definition (CDC 1989)

For reporting purposes, congenital syphilis includes cases of congenitally acquired syphilis in infants and children, as well as syphilitic stillbirths.

(Surveillance case definitions frequently have two categories, confirmed and presumptive; the distinction is usually based on the strength of the laboratory evidence. Cases in both categories should be reported.)

A confirmed case of congenital syphilis is an infant in whom *Treponema pallidum* is identified by darkfield microscopy, fluorescent antibody, or other specific stains in specimens from lesions, placenta, umbilical cord, or autopsy material.

A presumptive case of congenital syphilis is either of the following:

- A. Any infant whose mother had untreated or inadequately treated" syphilis at delivery, regardless of findings in the infant; or
- B. Any infant or child who has a reactive treponemal test for syphilis and any one of the following:
 1. any evidence of congenital syphilis on physical examination^b; or
 2. any evidence of congenital syphilis on long bone x-ray; or
 3. reactive cerebrospinal fluid (CSF) VDRL^c; or
 4. elevated CSF cell count or protein (without other cause)^c; or
 5. quantitative nontreponemal serologic

titres which are fourfold higher than the mother's (both drawn at birth): or

6. reactive test for FTA-ABS-19S-IgM antibody^c.

A syphilitic stillbirth is defined as a fetal death in which the mother had untreated or inadequately treated^a syphilis at delivery of a fetus after a 20-week gestation of >500 grams.

- a) Inadequate treatment consists of any non-penicillin therapy or penicillin given less than 30 days prior to delivery.
- b) Signs in an infant (<2 years) may include hepatosplenomegaly, characteristic skin rash, condylomata lata, snuffles, jaundice (syphilitic hepatitis), pseudoparalysis, or edema (nephrotic syndrome). Stigmata in an older child may include: interstitial keratitis, nerve deafness, anter-

ior bowing of shins, frontal bossing, mulberry molars, Hutchinson's teeth, saddle nose, rhagades, or Clutton's joints.

- c) It may be difficult to distinguish between congenital and acquired syphilis in a seropositive child after infancy. Signs may not be obvious and stigmata may not yet have developed. Abnormal values for CSF VDRL, cell count, and protein, as well as IgM antibodies, may be found in either congenital or acquired syphilis. Findings on long bone x-rays may help, since these would indicate congenital syphilis. The decision may ultimately be based on maternal history and clinical judgement; the possibility of sexual abuse also needs to be considered.